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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/719,988 | 11/20/2003 | Larry C. Mattheakis | CYTOP135X1 | 1753 |

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| EXAMINER | |
|---|---|
| SRIVASTAVA, KAILASH C | |
| ART UNIT | PAPER NUMBER |
| 1657 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 04/11/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/719,988 | MATTHEAKIS ET AL. | |
| | Examiner | Art Unit | |
| | Dr. Kailash C. Srivastava | 1657 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

# DETAILED ACTION

1. Applicants' responsive Amendment filed 16 January 2007 is acknowledged and entered. The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

2. In view of amendment filed 08 January 2007, objection to Claim 3 in the Office Action mailed 02 November 2006 is hereby withdrawn.

3. In view of remarks, Terminal Disclaimer under 37 C.F.R. §1.321 and amendment filed 08 January 2007, Obvious Type Double Patenting Rejection in the Office Action mailed 02 November 2006 is hereby withdrawn.

## CLAIMS STATUS

4. Claims 12-19 have been cancelled.

5. Claim 3 has been currently amended.

6. Claims 1-11 are pending and are examined on merits.

### Objection To Claims – Minor Informalities

7. Claims 1-2 and 11 are objected to because of the following informalities:

- In Claim 1 (a) at Line 2 the recitation, "extract" and in Claim 11 at line 1, the recitation, "extracted" do not clarify whether there is a mental consideration/steps taken with the images to get the hepatocyte-features from said images, or those recitations mean that the images are treated with a material (e.g., a solvent) to obtain the hepatocyte-features from said images. This is because, the art-known broadest interpretation of the recitation, "extract" or "extracted" is to treat a material with another material to take out some material from the material being treated (e.g., a cell culture comprising both cultivated cells and spent culture medium is treated with a solvent to take out a protein or a biologically produced product from the cell culture). Appropriate clarification/correction is required.

- In each of claim 1(b), and in Claim 11, the Markush groups for hepatotoxic pathologies and features, respectively are improperly recited. Appropriate recitation for said Markush groups is required.

- In Claim 2 at line one after the word "claim" the ", " (i.e., comma) seems to be grammatically incorrect.

- In Claim 6 at line one the recitation, "support cells" is unclear because it is not clear in what way those cells are supporting hepatocytes.

- In Claims 8-9 at line one the recitation, "immortalized" is unclear. Is this recitation similar to what is known in the art for describing "HeLa cell lines"? Metes and bounds for said term should be defined.

Appropriate corrections/clarifications are required.

## *Claim Rejections Under 35 U.S.C. §112*

8. The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> ***The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.***

9. Claims 2-6 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Limitation, "hepatocyte culture" at Claim 2, Line 2, renders Claim 2 unclear and indefinite because the limitation "hepatocyte culture" lacks sufficient antecedent basis. Claim 2 depends from Claim 1. Claim 1 recites "a method of assessing the hepatotoxicity of a stimulus, the method comprising: 1 (a) analyzing an image of hepatocytes that have been exposed to a stimulus". Appropriate correction is required.

- Limitation, "hepatocytes are co-cultured with support cells" in claim 6 renders Claim 6 unclear and indefinite because said limitation lacks sufficient antecedent basis. Claim 6 depends from Claim 3. Claim 3 recites, "multiple hepatocyte cultures are located on a single support structure..." There is no mention of co-culturing hepatocytes in Claim 3. Appropriate correction is required.

All other claims depend directly or indirectly from the rejected claims (e.g., Claim2) and are, therefore, also rejected under 35 U.S.C. §112, second paragraph for the reasons set forth above.

## *Claim Rejections – 35 U.S.C. § 102*

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> ***A person shall be entitled to a patent unless –***
>
> ***(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.***

11. Claims 1, 7 and 10-11 are rejected under 35 U.S.C. §102(b) as anticipated by Aljajeh et al. (Indian Childhood Cirrhosis-Like Liver Disease in an Arab Child. A Brief Report. 1994. Virchows Archiv, Volume 424, Pages 225-227).

Claims recite a method to assess hepatotoxicity of a stimulus via analyzing a hepatocyte image exposed to said stimulus to obtain information on hepatocytes, wherein said information manifests quantitative features to classify ≥1 hepatotoxic pathologies because of the stimulus, said pathologies being ≥1 among: apoptosis, cholestasis, cirrhosis, fibrosis, necrosis or steatosis. In said method, hepatocytes are exposed to chemical stimulus. Said hepatocyte images are analyzed in segments and manifested information is on membrane permeability and Golgi distribution among a variety of parameters.

Regarding Claims 1, 7 and 10-11, Aljajeh et al. teach methods to a chemical mediated stimulus hepatotoxicities, viz. cholestasis, fibrosis and necrosis in photo and micrographs obtained from photo and electron microscopic observation on hepatocytes in liver tissue of a patient. Said assessment, based on observed changes in hepatocyte organelle structure (e.g., cellular membrane and endoplasmic reticulum) demonstrated diagnosis of cholestasis, fibrosis and necrosis in photo and electron micrographs respectively (See, e.g., legend to Figure 2, Lines 3 and 5 and Abstract). Said necrosis and fibrosis (i.e., hepatotoxicities) were manifestations of effect of higher hepatic copper concentration (See, Page 727, Column 1, Lines 12-23). Photo and electron micrographs, inherently are images of the hepatocytes as observed in a photo, or an electron microscope. Aljajeh et al. also mention that hepatic copper concentrations were high in said patient. Clearly the abnormal hepatocyte morphology observed was because of said stimulus, which is inherently chemical stimulus. Also, please note that Aljaleh et al. describe ≥1 hepatotoxic pathologies based ≥1 hepatocyte features (i.e., membrane and endoplasmic

reticulum morphologies). Therefore, the prior art method clearly anticipates Applicants' claimed invention in Claims 1, 7 and 10-11

Therefore, the reference is deemed to anticipate the cited claims.

## *Claim Rejections Under 35 U.S.C. § 103(a)*

12. The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> ***A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.***

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § *102*(f) or (g) prior art under 35 U.S.C.§ 103(a).

14. Claims 1-7 and 10-11 are rejected under 35 U.S.C. § 103 (a) as obvious over combined teachings from Aljajeh et al. (Indian Childhood Cirrhosis-Like Liver Disease in an Arab Child. A Brief Report. 1994. Virchows Archiv, Volume 424, Pages 225-227) in view of Powers et al. (A Microfabricated Array Bioreactor for Perfused 3D Liver Culture. 2002. Biotechnology & Bioengineering, Volume 78, Pages 257-269) and further in view of Le Cluyse et al (Expression and Regulation of Cytochrome P450 Enzymes in Primary Cultures of Human Hepatocytes. Journal of Biochem Molecular Toxicology. 2000. Volume 4, Number 4, Pages 177-188).

Claims recite a method to assess hepatotoxicity of a stimulus via analyzing a hepatocyte image exposed to said image to obtain information on hepatocytes, wherein said information manifests quantitative features to classify ≥1 hepatotoxic pathologies because of the stimulus, said pathologies being ≥1 among: apoptosis, cholestasis, cirrhosis, fibrosis, necrosis or steatosis. In said method, hepatocyte cultures are exposed to varying quantities of said stimulus, said stimulus being a chemical, wherein multiple hepatocytes are located on a plastic or glass support and each culture is exposed to a distinct stimulus. Said images are analyzed on segments and manifested information is on membrane permeability, condensation etc. among a variety of parameters.

Regarding Claims 1-2, 7 and 10-11, teachings from Aljajeh et al. have been discussed *supra.* Note that Aljajeh et al., made those observations on liver tissue hepatocytes obtained from a patient. Intrinsically, said hepatocytes were in culture because by art- known definition a culture is cells grown in a solid or liquid medium. Hepatocytes in liver are in a solid medium surrounded by liquid and while there, hepatocytes grow. Thus, Aljajehet al's teachings encompass the limitation of exposing the hepatocyte culture to the stimulus. Aljajeh et al., do not explicitly demonstrate that the hepatocytes were in vitro, growing on a single support, wherein each in vitro culture is exposed to a distinct, different quantities of stimulus while on a glass or a plastic support, immortalized and co-cultured with support cells. To express ≥1 cytochrome P450 enzyme.

Regarding Claims 3-7, Powers et al. teach hepatocyte cultivation in a bioreactor housed with a support and cells are continuously perfused through the 3D tissue mass, the stimulus is perfusion of culture medium. Powers et al. further teach studying the behavior of primary rat hepatocyte culture comprised of hepatocytes and non-parenchymal cells (Abstract, Page 257, Column 2, Lines 49-52), wherein said culturing is in the macro bioreactor made of stainless steel equipped with a glass window and the millireactor made of polycarbonate, the two being separated by plastic scaffolds (Page 259, Column 1, Below Figure 2, Lines 12-20). Also note that the fluid shear of perfusion with the hepatocyte growth medium (HGM) is in range of <2 dyne $cm^2$ (Abstract and Page, 260, Column 1, Lines 1-3). Additionally Powers et al. demonstrate repeated *in situ* imaging of tissue structure with two photon microscopy (Abstract, Lines 43-46). Thus, teachings from Powers et al. encompass each of the components in instant claims 2-7, viz:

i. imaging hepatocytes;

ii. hepatocytes cultured on support structures;

iii. *in vitro* culture exposed to distinct stimuli (i.e., intrinsically range of perfusion <2 dyne $cm^2$) as the perfusion liquid flows down the culture the stimulus of chemical in dynes per $cm^2$ will be different through the 3D hepatocyte mass);

iv. A chemical is the stimulus to which the cells are exposed before imaging (i.e., perfusion with HMG);

v. hepatocytes co-cultured with support cells (i.e., the culture is primary hepatocyte where in the cells have been obtained from liver and are comprised of non-parenchymal and hepatocytes);

vi. intrinsically teach imaging of hepatotoxicity of a stimulus because Powers et al. teach that their bioreactor system is an "applicable platform for the studies of *in vivo*

physiology and pathology in an *in vitro* environment" (See Page 268, Column 1, Lines 53-56).

Regarding Claim 9, Cluyse et al. teach each and every limitation except for transforming a hepatocyte because they teach cultivation of human hepatocytes and induction of P450 enzymes in human hepatocytes cultivated in "sandwich" cultures in a number of culture media to observe P450 enzyme expression (Abstract, Lines 1-19; Page 178, Column 2, Line 48 to Page 179, Column 1, Line32).

A person of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the teachings from each one of Powers et al. and Cluyse et al. in to the teachings from Aljajeh et al., because as pointed out above, Aljajeh et al. teach a method of assessing the hepatotoxicity via analyzing the hepatocyte images to obtain information on chemical stimulus –mediated hepatotoxicity manifested by the alterations in hepatocyte organelle (e.g., cell membrane) structures, while owers et al. teach imaging hepatocyte cultured in a bioreactor wherein said bioreactor has facilities to cultivate in co-culture hepatocytes and support cells on scaffolds of plastic as a function of a chemical stimulus, wherein said imaging is applicable to assess hepatotoxicity (See, e.g., Page 268, Column 1, Lines 53-56). and Cluyse et al. teach expression of P450 enzymes in cultured hepatocytes in presence of a number of different chemical stimuli (Abstract, Lines 1-19; Page 178, Column 2, Line 48 to Page 179, Column 1, Line32).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of each one of Aljajeh et al., Powers et al., and Cluyse et al. to obtain a method to assess the hepatotoxicity of a chemical stimulus via analyzing images of hepatocytes cultured in presence of a chemical stimulus and observing altered manifestations in hepatocyte organelle, because Aljajeh et al. teach a method of assessing the hepatotoxicity via analyzing the hepatocyte images to obtain information on chemical stimulus–mediated hepatotoxicity manifested by the alterations in hepatocyte organelle (e.g., cell membrane) structures, while Powers et al. teach imaging hepatocyte cultured in a bioreactor wherein said bioreactor has facilities to cultivate in co-culture hepatocytes and support cells on scaffolds of plastic as a function of a chemical stimulus, wherein said imaging is applicable to assess hepatotoxicity and Cluyse et al. teach expression of P450 enzymes in cultured hepatocytes in presence of a number of different chemical stimuli. This rejection is based on the well established proposition of patent law that no invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients, *In re Sussman,* 1943 C.D. 518. Applicants invention is predicated on an unexpected result,

which typically involves synergism, an unpredictable phenomenon, highly dependent upon specific proportions and/or amounts of particular ingredients. Any mixture of the components embraced by the claims which does not exhibit an unexpected result (e.g., synergism) is therefore *ipso facto* unpatentable.

Accordingly, the instant claims, in the range of proportions where no unexpected results are observed, would have been obvious to one of ordinary skill having the above-cited references before him.

From the explanations of teachings of the cited references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. Claims 8-9 are rejected under 35 U.S.C. § 103 (a) as obvious over combined teachings from Aljajeh et al. (Indian Childhood Cirrhosis-Like Liver Disease in an Arab Child. A Brief Report. 1994. Virchows Archiv, Volume 424, Pages 225-227) in view of Powers et al. (A Microfabricated Array Bioreactor for Perfused 3D Liver Culture. 2002. Biotechnology & Bioengineering, Volume 78, Pages 257-269) and in view of Le Cluyse et al (Expression and Regulation of Cytochrome P450 Enzymes in Primary Cultures of Human Hepatocytes. Journal of Biochem Molecular Toxicology. 2000. Volume 4, Number 4, Pages 177-188) an further in view of Morel et al (1990, Expression of Cytochrome P-450 Enzymes in Cultured Human Hepatocytes, Eur. J. Biochem., Volume 191, Pages 437-333).

Claims 8-9 additionally recite that said hepatocytes are transformed and further modified to express ≥1 cytochrome P450 enzyme.

Teachings from Aljajeh et al., Powers et al. and Cluyse et al. have been discussed *supra*. The elements in Claims 8-9, especially in regard to transformed hepatocytes is not explicitly clear from those teachings. Morel et al. teach methods to transform cultured human primary culture hepatocytes to produce specific cytochrome P-4 50 IIIA and P-450 IIC8/9/10. The expression for individual P-450 products was induced via transforming human hepatocytes through cultivation in standard medium supplemented with each of rifampicin, 3-methylcholanthrene or Phenobarbital in separate flasks. Subsequently, with each medium change, the basic cell culture medium was consistently supplemented with the same inducing agent and the transformed hepatocytes were harvested after the third addition of inducers (Page 438, Column 1, Lines44-65 and cytochrome P-450 expression was assayed (Page 439, Column 1, Line 10 to Page 439, Column 2, Line 32).

A person of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the teachings from Morel et al, in to the combined teachings from each one of Powers et al., Cluyse et al. and Aljajeh et al., because as pointed out above, Aljajeh et al. teach a method of assessing the hepatotoxicity via analyzing the hepatocyte images to obtain information on chemical stimulus –mediated hepatotoxicity manifested by the alterations in hepatocyte organelle (e.g., cell membrane) structures, while Powers et al. teach imaging hepatocyte cultured in a bioreactor wherein said bioreactor has facilities to cultivate in co-culture hepatocytes and support cells on scaffolds of plastic as a function of a chemical stimulus, wherein said imaging is applicable to assess hepatotoxicity (See, e.g., Page 268, Column 1, Lines 53-56), Cluyse et al. teach expression of P450 enzymes in cultured hepatocytes in presence of a number of different chemical stimuli and Morel et al teach transformation of human hepatocytes in culture to express different cytochrome P-450 products depending upon the inducer for transformation.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of each one of Aljajeh et al., Powers et al., Cluyse et al. and Morel et al. to obtain a method to assess the hepatotoxicity of a chemical stimulus via analyzing images of hepatocytes cultured in presence of a chemical stimulus and observing altered manifestations in hepatocyte organelle, because Aljajeh et al. teach a method of assessing the hepatotoxicity via analyzing the hepatocyte images to obtain information on chemical stimulus –mediated hepatotoxicity manifested by the alterations in hepatocyte organelle (e.g., cell membrane) structures, while Powers et al. teach imaging hepatocyte cultured in a bioreactor wherein said bioreactor has facilities to cultivate in co-culture hepatocytes and support cells on scaffolds of plastic as a function of a chemical stimulus, wherein said imaging is applicable to assess hepatotoxicity, Cluyse et al. teach expression of P450 enzymes in cultured hepatocytes in presence of a number of different chemical stimuli and Morel et al. teach transformation of human hepatocytes by a variety of inducers to illicit expression of a different P-450 product. This rejection is based on the well established proposition of patent law that no invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients, *In re Sussman,* 1943 C.D. 518. Applicants invention is predicated on an unexpected result, which typically involves synergism, an unpredictable phenomenon, highly dependent upon specific proportions and/or amounts of particular ingredients. Any mixture of the components embraced by the claims which does not exhibit an unexpected result (e.g., synergism) is therefore *ipso facto* unpatentable.

Accordingly, the instant claims, in the range of proportions where no unexpected results are observed, would have been obvious to one of ordinary skill having the above-cited references before him.

From the explanations of teachings of the cited references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. For reasons aforementioned, no Claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (571) 272-0923. The examiner can normally be reached on Monday to Thursday from 7:30 A.M. to 6:00 P.M. (Eastern Standard or Daylight Savings Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached at (571)-272-0925 Monday through Thursday 7:30 A.M. to 6:00 P.M. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding may be obtained from the Patent Application Information Retrieval (i.e., PAIR) system. Status information for the published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (i.e., EBC) at: (866)-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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01 April, 2007

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